Structural–Functional Relationships of TNF-Alpha Antagonists: Next Steps

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The balance between effective tumor necrosis factor (TNF) blockade to control aggressive autoimmune disease states and adequate remaining TNF activity to confer immunoprotection against infections such as tuberculosis is an important and complex issue. An increased scientific understanding of how each of the TNF antagonist agents affects the complex interactions of the inflammation cascade and apoptosis, and whether the effects are modulatory or destructive, is needed. The data presented in this supplement highlight the need for further research into these key areas, and illustrate our current understanding of the mode of action of TNF blockers as only the tip of the iceberg.

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There remain many unanswered questions regarding tumor necrosis factor (TNF) antagonists and their effects on the immune system and the patient. Although neutralizing TNF can alleviate symptoms of inflammatory diseases, there appear to be implications for patients' susceptibility to infections such as tuberculosis. Many of the immune-related diseases have been associated with elevated levels of TNF, but as the animal models with deleted genes presented suggest, levels of TNF that are insufficient may compromise innate immunity and confer greater risks of infections. It may be that therapies that neutralize TNF bioactivity completely, while potentially active in a wider range of diseases, move TNF levels below an immunoprotective window. The relative importance of serum versus tissue concentrations of TNF is also unknown, and whether this varies in different disease states and even different tissues. And, although TNF is a major cytokine that is involved in a number of inflammatory diseases, there are obviously other immunomodulatory cytokines of which the same questions should be asked – IFN-γ, IL-12, IL-23, IL-15, and lymphotoxin-α, while clearly important, have roles that need further elucidation.

Perhaps, a better understanding of the differences between the two classes of anti-TNF therapies might also provide clues as to the mechanisms behind these inflammatory diseases, as well as the susceptibility to bacterial and opportunistic infections. The elucidation of the crystallographic structures has shed light onto the potential interactions between TNF and fusion protein or antibody, but many questions remain unanswered. For example, the finding by Kohno *et al.* (published in this supplement) that, *in vitro*, the anti-TNF monoclonal antibodies formed large complexes with TNF whereas the fusion protein did not, has yet to show clinical implications; does this mean that the relevance of the complexes might only be in mediating cell death by antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity, or are there other implications that are undiscovered as yet? Cell death and apoptosis both need further exploration; whereas TNF receptor p55 and, to a lesser extent, p75 are known to be involved, the multiple and complicated interactions between the two TNF cell-surface receptors are also not understood fully.

Data reviewed in this supplement suggested that tuberculosis risk might be associated with inhibition of T cell activation and IFN-γ production, but not with effects on IL-10. What is the basis for these cytokine-specific downstream effects? Are they mediated by binding to soluble or membrane-associated TNF? Is their locus the T cell or the antigen-presenting cell? If the T cell, do TNF antagonists alter the ability of T cells to recognize and respond to foreign antigen, and do the two classes of TNF antagonists have different effects? Two reports have indicated that TNF antagonists induce regulatory T cells (Wu *et al.*, 2002; Ehrenstein *et al.*, 2004), but is this finding sufficient to explain the susceptibility to infections with intracellular pathogens? There are other activities that need to be examined, including the role of TNF-α antagonists on antigen presentation and on

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the induction of cytokines that may block the expression of cellular immunity.

Optimal strategies to prevent and manage infectious complications of TNF blockade remain incompletely defined. For example, Kaur and Mahl (in press) have identified 84 cases of *Pneumocystis jiroveci (carinii)* pneumonia in patients with inflammatory bowel disease treated with infliximab. Although the cases appear to be infrequent, a mortality rate of 27% has been reported (Kaur and Mahl; T Mahl (Personal communication with R Wallis)). Prophylaxis with trimethoprim-sulfa has been highly effective in preventing *Pneumocystis* pneumonia in persons with HIV infection. Presently, there are no strategies for screening and/or prevention of fungal infections such as histoplasmosis and coccidioidomycosis. Even for tuberculosis, a complication for which the relative risks of the TNF blockers have been best defined, and for which screening and prophylaxis has been most successful, many questions remain. If tuberculosis is diagnosed and anti-TNF therapy is discontinued, how quickly must it be stopped and when may it be resumed? Will existing strategies be effective in regions of high, ongoing tuberculosis transmission? These questions will become increasingly important as these drugs become available globally.

Considerations relevant to patients with inflammatory diseases are not limited to infections, of course. Other potentially important fields of study are the effect of TNF blockade on related diseases such as inflammatory-mediated cardiovascular disease, metabolic syndrome, or psoriatic arthritis; is it possible to affect the likelihood of developing these related diseases by treating an existing inflammatory disorder with TNF blockade? To optimize patient care, it would be beneficial to develop clinically practical assays that measure concentration of drug, gene regulation in cells and tissues, and/or biomarkers in serum to predict clinical response to TNF blockade or to identify patients likely to experience adverse events. As the population of patients who are treated by TNF antagonism expands, it will also be critical to further understand the effect of TNF blockade, if any, on neonates and children.

It is striking that these basic questions regarding mechanism of action are still being studied 8 years and 1 million treated patients after these drugs were first approved. However, one anticipates that the ongoing characterization of the differential actions of the TNF antagonists may continue to contribute to our understanding of the diverse clinical outcomes. Translational research – the process of moving from clinical signal to molecular underpinnings, and back again – requires a continued dialogue between the clinician and the scientist. Learning why and how will ensure the best care for patients who live with these chronic diseases.

CONFLICT OF INTEREST

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